6. (Amended) A method according to claim 2, wherein said agent is administered prior to said heterologous protein and/or said nucleic acid sequence encoding said heterologous protein.

8. (Amended) A method according to claim 7, wherein said agent and said nucleic acid sequence encoding said heterologous protein are simultaneously co-administered as a recombinant virus, the genome of which comprises at least one nucleic acid sequence encoding said heterologous protein.

9. (Amended) A method according to claim 8, wherein the genome of said recombinant virus comprises at least regulatory sequences necessary to direct the expression of said heterologous protein in at least one antigen presenting cell of said mammal.

10. (Amended) A method according to claim 9, wherein said regulatory [regulation] sequences comprises promoter sequences selected from the group consisting of [among] cytomegalovirus early promoter (CMV IEP), Rous sarcoma virus long terminal repeat promoter (RSV LTR), myeloproliferative sarcoma virus long terminal repeat (MPSV LTR), simian virus 40 early promoter (SV40 IEP), and major late promoter of the adenovirus.

11. (Amended) A method according to any one of claims 1 to 10, further comprising administering to said mammal an additional agent to enhance the depletion and/or the inhibition of at least some antigen presenting cells of said mammal.

12. (Amended) A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein comprising administering to said mammal a recombinant adenovirus, the genome of which comprises at least a nucleic acid sequence encoding said heterologous protein and regulatory sequences, in an amount sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, thereby inhibiting the production of neutralizing antibodies against said heterologous protein.

13. (Amended) A method according to claim 12, further comprising administering to said mammal additional adenovirus or a fragment thereof, the genome of which <u>is</u> not expressing said heterologous protein, thereby enhancing the amount of adenoviruses to deplete or inhibit at least some antigen presenting cells of said mammal.

14. (Amended) A method according to any one of claims 12 to 13, wherein said mammal is a mouse and wherein the amount of adenovirus particules administered to deplete

or inhibit at least some antigen presenting cells of said mouse is equal or greater to 4.10^{10} particles, said particles comprising optionally said additional adenovirus.

16. (Amended) A method according to any one of claims 14 to 15, wherein the amount of said recombinant adenovirus able to form plaque, is equal or greater to 4.10^{9} pfu/mouse.

19. (Amended) A method for reducing an anti-heterologous protein immune response in a mammal, including human, subject to the administration of said heterologous protein and/or nucleic acid sequence encoding said heterologous protein, said method comprising inhibiting in said mammal the formation of neutralizing antibodies directed against said heterologous protein by the method according to any one of claims 1 to 16.

21. (Amended) A method for therapy of a mammal, including humans, afflicted with a disease characterized by the altered expression of an endogenous protein, said method comprising administering to said mammal said protein and/or nucleic acid sequence encoding said protein, and simultaneously or previously, the step of inhibiting in said mammal formation of neutralizing antibodies directed against said protein by the method according to any one of claims 1 to 16.

22. (Amended) A method according to any one of claims 20 and 21, further comprising co-administering simultaneously, separately or sequentially, to said mammal at least one immune modulator selected from the group consisting of cyclosporin, cyclophosphamide, FK506, desoxyspergualine, interleukin-4, interleukin-12, interferon-gamma, anti-CD4 monoclonal antibody, anti-CD8 monoclonal antibody, anti-LFA1 monoclonal antibody, and antibody directed against CD40 ligand or CTLA4Ig.

27. (Amended) A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein, said method comprising:

(i) Optionally, co-administering to a first mammal, at least one agent and said heterologous protein and/or a nucleic acid sequence encoding said heterologous protein, said agent being administered simultaneously, sequentially or separately with said heterologous protein and/or nucleic acid sequence, and determining at least one amount of said heterologous protein and said agent, sufficient to trigger an immune response against said

heterologous protein by said first mammal; optionally, re-performing step (i) until said amount is determined;

(ii) co-administering to a second mammal said heterologous protein and/or nucleic acid sequence encoding said heterologous protein, in an amount sufficient to trigger an immune response against said heterologous protein, as determined at step (i) and prior to or simultaneously administering said agent, in an amount greater that the one determined at step (i) and sufficient to trigger an immune response against said agent and sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and determining for said second mammal at least one amount of said agent that reduces and/or suppresses the anti-heterologous protein immune response in said mammal; re-performing step (ii) until said amount is determined; and wherein when one co-administers to said mammal said heterologous protein and/or nucleic acid sequence encoding said heterologous protein, and prior to or simultaneously with an agent in an amount equal to or greater than the one determined at step (ii), said mammal produces neutralizing antibodies against said agent but produces no or few neutralizing antibodies against said heterologous protein.

29. (Amended) A method for therapy of a mammal affected by a disease wherein at least one endogenous protein is involved in said disease etiology, said method comprising inhibiting the biological functions of said endogenous protein by enhancing the production of neutralizing antibodies against said protein by use of the method according to claim 23.

30. (Amended) A method according to claim 29, wherein said disease is selected from the group consisting of auto-immune diseases, inflammatory diseases, cancers, viral infections, bacterial infections, parasitic infections, and fungal infections.

43. (Amended) A method according to any one of claims 1 to 26 and 33, wherein said heterologous protein or a fragment thereof is selected from the group consisting of the proteins that are presented by class I major histocompatibility molecule (CMH I), a class II major histocompatibility molecule (CMH II), and a combination of a class I major histocompatibility molecule and a class II major histocompatibility molecule.

44. (Amended) A method according to claim 43, wherein said heterologous protein is selected from the group consisting of secreted proteins, membrane proteins, receptors, intracellular proteins, and nuclear proteins.

45. (Amended) A method according to claim 44, wherein said secreted protein is selected from the group consisting of neuromediators, hormones, interleukines, lymphokines, interferons, chemokines, and growth factors.

46. (Amended) A method according to any one of claims 1 to 26 and 33, wherein the mammal is selected from the group consisting of mouse, rat, rabbit, hamster, pig, cow, goat, sheep, horse, and primate.

47. (Amended) A method according to any one of claims 1 to 26 and 33, wherein the administration of said agent and said heterologous protein and/or nucleic acid sequence encoding said heterologous protein is performed via a technique selected from the group consisting of intravenous injection, intravaginal injection, intrarectal injection, intramuscular injection, and intradermic injection.

Please add the following new claims:

49. (New) A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein comprising co-administering to said mammal, an agent in an amount sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and a nucleic acid sequence encoding said heterologous protein, said agent being administered prior to or simultaneously with said nucleic acid sequence, thereby inhibiting the production of neutralizing antibodies against said heterologous protein.

50. (New) A method according to claim 49, wherein said agent is selected among viruses, liposomes, antibodies, parasites, bacteria, funguses and or fragments thereof, and nucleic acid sequence encoding said heterologous protein.

51. (New) A method according to claim 50, wherein said virus is selected from the group consisting of adenovirus, adeno-associated virus, retrovirus, pox virus, vaccinia virus, and fragments thereof.

52. (New) A method according to claim 51, wherein said adenovirus is selected from the group consisting of wild type human adenovirus, recombinant adenovirus, and a fragment thereof.

53. (New) A method according to claims 49, wherein said antigen presenting cells are antigen presenting cells located in liver of said mammal.

54. (New) A method according to claim 50, wherein said agent is administered prior to said nucleic acid sequence encoding said heterologous protein.

55. (New) A method according to claim 50, wherein said agent is administered simultaneously to said nucleic acid sequence encoding said heterologous protein.

56. (New) A method according to claim 55, wherein said agent and said nucleic acid sequence encoding said heterologous protein are simultaneously co-administered as a recombinant virus, the genome of which comprises at least nucleic acid sequence encoding said heterologous protein.

57. (New) A method according to claim 56, wherein the genome of said recombinant virus comprises at least regulatory sequences necessary to direct the expression of said heteroloqous protein in at least one antigen presenting cell of said mammal.

58. (New) A method according to claim 57, wherein said regulation sequences comprises promoter sequences selected from the group consisting of cytomegalovirus early promoter (CMV IEP), Rous sarcoma virus long terminal repeat promoter (RSV LTR), myeloproliferative sarcoma virus long terminal repeat (MPSV LTR), simian virus 40 early promoter (SV4O IEP) and major late promoter of the adenovirus.

59. (New) A method according to claims 49, further comprising administering to said mammal additional agent to enhance the depletion and/or the inhibition of at least some antigen presenting cells of said mammal.

60. (New) A method for reducing an anti-heterologous protein immune response in a mammal, including human, subject to the administration of said nucleic acid sequence encoding said heterologous protein, said method comprising inhibiting in said mammal formation of neutralizing antibodies directed against said heterologous protein by the method according to claim 49.

61. (New) A method according to claim 60, wherein said method is a step of a gene therapy protocol for the treatment of human afflicted with a disease selected from the group consisting of inherited or acquired genetic diseases, infectious diseases, inflammatory diseases, autoimmune diseases, cancers, and associated syndromes thereof.

62. (New) A method for the therapy of a mammal, including humans, afflicted with a disease characterized by the altered expression of an endogenous protein, said method

comprising administering to said mammal said nucleic acid sequence encoding said protein, and simultaneously or previously, the step of inhibiting in said mammal formation of neutralizing antibodies directed against said protein by the method of claims 12-16 and 49-59.

63. (New) A method according to claims 61 and 62, further comprising co-administering simultaneously, separately or sequentially, to said mammal at least one immune modulators selected from the group consisting of cyclosporin, cyclophosphamide, FK506, desoxyspergualine, interleukin-4, interleukin-12, interferon-gamma, anti-CD4 monoclonal antibody, anti-CD8 monoclonal antibody, anti-LFAI monoclonal antibody, and antibody directed against CD40 ligand or CTLA4Ig.

64. (New) A method of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein, said method comprising:

(i) Optionally, co-administering to a first mammal, at least one agent and a nucleic acid sequence encoding said heterologous protein, said agent being administered simultaneously, sequentially or separately with said nucleic acid sequence, and determining at least one amount of said heterologous protein and said agent, sufficient to trigger an immune response against said heterologous protein by said first mammal; optionally, re-performing step (i) until said amount is determined;

(ii) co-administering to a second mammal said nucleic acid sequence encoding said heterologous protein, in an amount sufficient to trigger an immune response against said heterologous protein, as determined at step (i) and prior to or simultaneously administering said agent, in an amount greater that the one determined at step (i) and sufficient to trigger an immune response against said agent and sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and determining for said second mammal at least one amount of said agent that reduces and/or suppresses the anti-heterologous protein immune response in said mammal; re-performing step (ii) until said amount is determined; and wherein when one co-administers to said mammal said nucleic acid sequence encoding said heterologous protein, and prior to or simultaneously with an agent in an amount equal or greater than the one determined at step (ii), said mammal produces neutralizing antibodies against said agent but produces no or few neutralizing antibodies against said heterologous protein.

65. (New) A method for the therapy of a mammal affected by a disease wherein at least one endogenous protein is involved in said disease etiology, said method comprising inhibiting the biological functions of said endogenous protein by enhancing the production of neutralizing antibodies against said protein by use of a method of modulating in a mammal formation of neutralizing antibodies directed against a heterologous protein, said method comprising:

(a) optionally, co-administering to a first mammal, at least one agent and a nucleic acid sequence encoding a heterologous protein, said agent being administered simultaneously, sequentially or separately with said nucleic acid, and determining at least one amount of said heterologous protein and said agent, sufficient to trigger an immune response against said heterolgous protein by said first mammal; optionally, re-performing step (a) until said amount is determined;

(b) co-administering to a second mammal said nucleic acid sequence encoding said heterologous protein, in an amount sufficient to trigger an immune response against said heterologous protein, as determined at step (a) and prior or simultaneously, said agent, in an amount greater than the one determined in step (a) and sufficient to trigger an immune response against said agent and sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and determining for said second mammal at least one amount of said agent that reduces and/or suppresses the anti-heterologous protein immune response in said mammal; re-performing step (b) until said amount is determined; and wherein

(c) when one administers to a third mammal, said agent in an amount equal or greater than the one determined at step (a) but lesser than the one determined at step (b), said mammal produces neutralizing antibodies against said heterologous protein and optionally against said agent; and one administers to said mammal said agent in an amount equal or greater than the one determined at step (b), said mammal produces neutralizing antibodies against said agent but produces no or few neutralizing antibodies against said heterologous protein.

66. (New) A method according to claim 65, wherein said disease is selected from the group consisting of auto-immune diseases, inflammatory diseases, cancers, viral infections, bacterial infections, parasitic infections and fungal infections.

67. (New) A method according to claim 12, wherein said heterologous protein or a fragment thereof is selected from the group consisting of the proteins that are presented by class I major histocompatibility molecule (CMH I), a class II major histocompatibility molecule (CMH II), and a combination of a class I major histocompatibility molecule and a class II major histocompatibility molecule.

68. (New) A method according to claim 67, wherein said heterologous protein is selected from the group consisting of secreted proteins, membranes proteins, receptors, intracellular proteins, and nuclear proteins.

69. (New) A method according to claim 68, wherein said secreted protein is selected from the group consisting of neuromediators, hormones, interleukines, lymphokines, interferons, chemokines, and growth factors.

70. (New) A method according to claim 12, wherein the mammal is selected from the group consisting of mouse, rat, rabbit, hamster, pig, cow, goat, sheep, horse, and primate.

71. (New) A method according to claim 12, wherein the administration of said agent and said nucleic acid sequence encoding said heterologous protein is performed via a technique selected from the group consisting of intravenous injection, intravaginal injection, intrarectal injection, intramuscular injection, and intradermic injection.

72. (New) A method according to claim 64, wherein an additional agent is further administered to said mammal in step (i) and (ii).

73. (New) A method according to any one of claims 64 and 72, wherein the amount of said agent of step (ii) is at least twice the amount of said agent determined at step (i).

74. (New) A method according to claim 64, wherein said mammal is a mouse and said agent is a virus selected from the group consisting of adenovirus, adenovirus associated virus, retrovirus, pox virus, and vaccinia virus, and wherein said agent and said nucleic acid sequence encoding said heterologous protein are simulatenously co-administered as a recombinant virus, the genome of which comprising at least said nucleic acid sequence encoding said heterologous protein.

75. (New) A method according to claim 64, wherein said mammal is a human and said agent a virus selected from the group consisting of adenovirus, adenovirus associated

virus, retrovirus, pox virus, and vaccinia virus, and wherein said agent and said nucleic acid sequence encoding said heterologous protein are simulatenously co-administered as a recombinant virus, the genome of which comprising at least said nucleic acid sequence encoding said heterologous protein.

76. (New) A method according to claims 74 or 75 wherein the recombinant virus is a recombinant adenovirus.

77. (New) A method according to claim 76 wherein the heterologous protein encoded by said recombinant adenovirus is a secreted protein.

78. (New) A method according to claim 77 wherein the nucleic acid sequence encodes the human thrombopoietin.

79. (New) A method according to claim 78 wherein the human thrombopoietin gene is under the control of the RSV promoter (AdRSVhuTPO).

80. (New) A method of inhibiting in a mouse formation of neutralizing antibodies directed against an heterologous protein, said method comprising:

(i) optionally, administering to a first mouse, a recombinant adenovirus, the genome of which comprising at least a nucleic acid sequence encoding said heterologous protein, and determining the amount of recombinant adenovirus particles that triggers an immune response towards said heterologous protein in said mouse without depleting or inhibiting at least some antigen presenting cell of said mouse, wherein:

(a) said amount of recombinant adenovirus particles is below 4.10^{10} particles, and/or

(b) the amount of said adenovirus particles able to form plaque is below 4.10^{9} pfu/mouse;

and optionally, re-performing step (i) until said amount is determined;

(ii) administering to a second mouse an amount of recombinant adenovirus particles in an amount greater that the one determined at step (i) and sufficient to trigger an immune response against said recombinant adenovirus particles and sufficient to deplete or inhibit at least some antigen presenting cells of said mouse, and determining for said second

mouse at least one amount of said recombinant adenovirus particles that reduces and/or suppresses the anti-heterologous protein immune response in said mouse, wherein:

(a) said amount of recombinant adenovirus particles is at least equal or greater than 4.10^{10} particles, and/or

(b) the amount of said adenovirus particles able to form plaque is equal or greater than 4.10^{9} pfu/mouse;

and optionally re-performing step (ii) until said amount is determined;

wherein when one administers to said mouse said recombinant adenovirus particles in an amount equal or greater than the one determined at step (ii), said mouse produces neutralizing antibodies against said adenovirus but produces no or few neutralizing antibodies against said heterologous protein.

81. (New) A method according to claim 80, wherein an additional agent is further administered to said mouse in step (i) and (ii).

82. (New) A method according to any one of claims 80-81, wherein the amount of said recombinant adenovirus particles of step (ii) is at least twice the amount of said recombinant adenovirus particles determined at step

83. (New) A method according to claim 12, wherein said heterologous protein or a fragment thereof is selected from the group consisting of the proteins that are presented by class I major histocompatibility molecule (CMH I), a class II major histocompatibility molecule (CMH II), and a combination of a class I major histocompatibility molecule and a class II major histocompatibility molecule.

84. (New) A method according to claim 83, wherein said heterologous protein is selected from the group consisting of secreted proteins, membranes proteins, receptors, intracellular proteins, and nuclear proteins.

85. (New) A method according to claim 84, wherein said secreted protein is selected from the group consisting of neuromediators, hormones, interleukines, lymphokines, interferons, chemokines, and growth factors.

86. (New) A method according to claim 12, wherein the mammal is selected from the group consisting of mouse, rat, rabbit, hamster, cow, pig, goat, sheep, horse, and primate.